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Roche

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BY HAND DELIVERY

Dockets Management Branch (HFA-305)
U.S. Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket 98P-1075; Ticlopidine Hydrochloride

Dear Sir/Madam:

On behalf of Hoffmann-La Roche Inc. (hereinafter referred to as "Roche" or the "company") I am writing to follow up on our Citizen Petition, filed November 27, 1998, Docket 98P-1075, and to restate our request for a meeting with the Food and Drug Administration ("FDA") to discuss the important issues raised in that petition, namely the public health need for a broad postmarketing safety program implemented by all manufacturers of ticlopidine. In addition, in light of recent events regarding this product, I am replying to the response filed with FDA on January 6, 1999, by Teva Pharmaceuticals USA Inc. (hereinafter referred to as "Teva") to Roche's Citizen Petition. In that Citizen Petition, Roche requested that FDA require that all manufacturers of ticlopidine hydrochloride implement a postmarketing safety program to ensure the continued safe marketing of this product. While Teva's response contains many inaccuracies and reflects an apparent disregard for the safety issues regarding ticlopidine, Roche believes that the proper focus of all interested parties is on the public health value of the program. Accordingly, set forth below is a description of our current postmarketing safety program and its contribution to public health.

98P-1075

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I. Background

The background on the program, including FDA's involvement with the program, is laid out in detail in the Citizen Petition and will not be repeated at length here. In brief, however, as FDA knows, since Ticlid was approved, Roche has maintained a postmarketing safety program composed of two elements: (1) a program of educational materials, provided to both physicians and patients, in addition to the approved professional labeling/package insert ("PI") and the patient package insert ("PPI") and (2) a blood monitoring program free to those patients who are unable to pay for such monitoring. These educational materials/labeling further educate and remind health professionals and patients of the critical need to monitor a patient's blood during the first three months of treatment with ticlopidine and to recognize the signs and symptoms of neutropenia and thrombotic thrombocytopenic purpura ("TTP"). The reason for this is simple: to further enhance the safe use of this vitally important therapeutic product.

Ticlid is indicated to reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors and in patients who have had a completed thrombotic stroke. Balanced against this significant benefit are two recognized health risks: neutropenia/agranulocytosis and TTP. Compliance with the required monitoring of a patient's blood during the first three months of ticlopidine therapy can indicate whether either of these fatal conditions is developing. The need for monitoring is described in the Ticlid PI and PPI. The postmarketing safety program goes beyond the information included in the PI and PPI by providing valuable repetition of the important safety messages. The components of the education program discuss in further detail such topics as stroke, TIA and ministrokes, the clinical signs and symptoms of neutropenia and TTP and the need to notify one's physician if these symptoms emerge, why CBC monitoring is required, and the need to comply with the CBC monitoring even if therapy is discontinued. In addition, utilization of the Roche sales force to implement this program allows for frequent and proactive dialogue and discussion. Such health education and monitoring programs are increasingly considered a vital part of the safe use of drugs by FDA and manufacturers.

On November 27, 1998, Roche filed its Citizen Petition with FDA requesting that the agency require all manufacturers of ticlopidine to implement a postmarketing safety program similar to that carried out by Roche since late 1991/early 1992 when Ticlid was approved. What follows is a brief review of the extensive nature of our program and its public health value as well as a response to some of the unfounded allegations propounded by Teva.

II. Roche Has Consistently Maintained a Postmarketing Program Since Ticlid Was Approved

A. Roche's Postmarketing Safety Program is Active

Throughout its submission, Teva asserts that Roche's program is too small or too hard to find. Such a claim is unfounded. In fact, just since 1995, when Roche assumed the marketing obligations for Ticlid, Roche sales representatives have ordered well over one million pieces of educational material 1/ for distribution in connection with this program. Based on the distribution practices of our sales force, we believe that these materials were distributed to approximately 60,000 physicians who prescribe Ticlid--usually is connection with a full presentation regarding Ticlid, including a focus on the required monitoring-- and, subsequently, to patients.

In addition, since 1992, Roche has provided for complete blood counts ("CBCs") for thousands of people. While patients taking Ticlid may qualify for third party reimbursement for these tests, in the event that they do not, the Roche program is available. Since 1992, Roche has paid for over 52,800 complete blood count ("CBC") tests. As this demonstrates, the Roche programs are hardly obscure and, indeed, further support the safety of the patients taking Ticlid.

Despite Teva's claims to the contrary, the Roche postmarketing safety program actively delivers educational materials to both patients and health professionals and provides CBC monitoring to those in need. Additional details regarding the monitoring and education programs are contained in Attachments A and B, respectively, to this document.

B. Roche's Postmarketing Safety Program Has a Long History

In its submission to the docket, Teva alleges that the postmarketing safety program is something Roche concocted to avoid generic competition. The postmarketing safety program is not new, however. It has been continuously run since shortly after Ticlid was approved in 1991 and is something in which FDA has been involved on an ongoing basis. Indeed, FDA has been instrumental in the implementation and maintenance of the program.

1/ Throughout this document Roche refers to the materials distributed in connection with the postmarketing safety program as "educational materials." Roche recognizes that certain of the educational materials also have promotional elements. See Section II.D.

Moreover, Roche did not raise the issue of the postmarketing safety program with respect to generics at the eleventh hour. Roche first raised the issue with the agency nearly a year and a half ago and has followed up with numerous pieces of correspondence and a meeting with the agency. Indeed, nearly six months ago in a submission to FDA Roche offered suggested guidelines on what all ticlopidine postmarketing safety programs should include (and offered to meet with the prospective manufacturers of generic ticlopidine on this issue). Accordingly, no aspect of this issue is new to the agency.

C. Roche's Postmarketing Program is Easily Accessible

Teva claims they "search[ed] systematically" and were unable to find information regarding the Ticlid postmarketing safety program. There were two options available to Teva to obtain information regarding the Ticlid postmarketing safety program, which included direct contacts at Roche who would provide any ticlopidine ANDA holder with information regarding the postmarketing safety program and a toll free number where ANDA holders, physicians and patients could also obtain such information regarding Ticlid. At the specific request of FDA, Roche provided the Office of Generic Drugs, with the names and phone numbers of the two contacts at Roche who would provide and/or were ready to discuss with any ANDA holder detailed information regarding the postmarketing safety program. Teva did not contact either of these individuals.

We do believe that Teva did call the toll free number given that they claim in their response to Roche's Citizen Petition that a caller placed several calls to Roche on Teva's behalf regarding the postmarketing safety program and the caller did not receive answers that he deemed to be satisfactory. Roche finds this claim puzzling. However, it provides us with the opportunity to explain how such calls are handled and describe the breadth of our programs. Currently, and at the time the calls allegedly were placed, Roche has in place a state-of-the-art product information system. Calls generally are made to the Department of Product Information within the Department of Medical Affairs. Calls are answered by registered nurses ("RNs") who are equipped with voluminous amounts of information regarding Roche products, including Ticlid, much of which is available through a computer information system with current information. Nurses are trained to answer all questions if they are able. If an RN receives a question that he or she is unable to answer, the nurse refers the question to a Product Services Manager ("PSM"), all of whom are health care professionals such as pharmacists and nurses. The PSM would then answer the inquiring party's question at that time or find the necessary information and get back to the inquiring party.

It is Roche's belief that the Department of Product Information provides all callers with first class service and proper product information, including if requested, information about the monitoring program. Since November 2, 1998, the Roche Department of Product Information has received over 2,327 calls regarding Ticlid and while Teva did not provide the name of the party who called on their behalf, Roche's records indicate that a pharmacist called on December 2, 1998--the date on which Teva says it became aware of the petition and conferred with a pharmacist regarding the program--inquiring about the CBC monitoring program. Based on our records, we believe that, like any pharmacist that inquires about this program, he was provided with the phone number to the SmithKline Beecham Ticlid Project Center line, which would have provided the pharmacist with all of the details regarding registering for the CBC monitoring program.

D. The Roche Educational Materials Go Beyond Promotion and Fair Balance

Teva argues that the Roche materials are not educational in nature but are promotional materials with an element of fair balance. Certainly, because they often discuss safety and efficacy, most materials that any drug company distributes to health professionals and patients have a promotional element. However, the important distinction between these materials and materials that are solely promotional is that they go well beyond promotion. For example, they remind their intended audience--including the medical community--of the risks associated with taking Ticlid, neutropenia and TTP, and the signs and symptoms thereof, as well as the critical need for blood monitoring to assure safe use. They also address stroke, TIAs, mini-strokes, approved indications for Ticlid, hematological safety, and safety generally. Further, as per 21 C.F.R. § 314.81, all of the Ticlid educational materials have been submitted to FDA's Division of Marketing, Advertising, and Communication for their review.

Roche believes that the keys to success in providing these valuable and potentially life-saving educational efforts are that they have broad reach, are continuous in nature and are provided through several vehicles that facilitate proactive dialogue. Rather than accept Teva's unsubstantiated allegations regarding these materials, Roche is proud of these materials which directly address the safety of the patient and further enhance the safe use of Ticlid. Based on its submission, Teva apparently does not fully comprehend the safety issues involved or simply is not willing to acknowledge the same.

III. The Relevant Statutes Provide FDA with Ample Authority

The Roche Citizen Petition describes the applicable statutes in detail and it is unnecessary to repeat that discussion here. The critical point is that all drugs approved pursuant to section 505(b)of the Federal Food, Drug, and Cosmetic Act (the "Act"), 21 U.S.C. § 201 et seq., must be safe and effective. While it is true that new drug applications are approved pursuant to section 505(b) of the Act, 21 U.S.C. § 355(b), and abbreviated new drug applications are approved pursuant to section 505(j), 21 U.S.C. § 355(j), the statutory standards are intertwined. Once conditions of use are determined for a new drug pursuant to section 505(b), a generic applicant must submit an application that includes, among other things, "information to show that the conditions of use prescribed, recommended or suggested in the labeling proposed for the new drug have been previously approved for a drug listed under paragraph (6) (hereinafter in this subsection referred to as a 'listed drug')". Id. § 355(j)(2)(A)(i). See also 21 U.S.C. § 355(j)(2)(A)(v) (containing the requirement that the products bear the same labeling). Thus, there is no doubt that the conditions of use necessary to assure safety and efficacy must be the same for both a new drug and a generic drug. Accordingly, the conditions of use for a ticlopidine product approved pursuant to an NDA and those approved pursuant to an ANDA must be the same.

Further, with regard to the misbranding provisions of the law fully discussed in the Citizen Petition, these provisions apply equally to all drug products irrespective of their approval status. Under these circumstances, judicial decisions requiring FDA to apply standards equally are fully applicable to this situation. Bracco Diagnostics, Inc. v. Shalala, 963 F. Supp. 20 (D.D.C. 1997) (agency acted arbitrarily and capriciously, and violated the APA, where it subjected two similar products to different approval standards). See also Independent Petroleum Assoc. of American v. Babbitt, 92 F.3d 1248 (D.C. Cir. 1996); Airmark Corp. v. FAA, 758 F.2d 685 (D.C. Cir. 1985) (citation omitted); U.S. v. Dialpulse Corp., 748 F.2d 56, 62 (2d Cir. 1984).

IV. Conclusion

Because Teva's lack of understanding of the purpose and scope of Roche's postmarketing safety program is apparent throughout its submission to the docket, Roche must question Teva's motivation for its position on the necessity of a postmarketing program. The inaccurate nature of its response belies Teva's real concern: its reluctance or inability to implement a postmarketing safety program which FDA has deemed essential to the safe use of the product.

Quite properly, FDA's focus in this matter should be whether all patients taking ticlopidine should have the benefit of continuously informed and educated physicians and a postmarketing safety program with minimum requirements to be met by all manufacturers. It is our belief that the program enhances the safe use of the product and should be required of all manufacturers.

If you have any questions or would like any additional information, please do not hesitate to contact me.

Sincerely,

HOFFMANN-LA ROCHE INC.

Frederick C. Kentz, III by RPB

Frederick C. Kentz
Vice President and General Counsel
973-235-2165

Attachments

cc: Dr. Janet Woodcock - CDER/Director
Dr. Robert Temple - CDER
Dr. Raymond Lipicky - DCRDP
Dr. Robert Fenichel - DCRDP
Dr. Stephen Fredd - DCRDP
Mr. Douglas Sporn - OGD
Mr. Robert West - OGD
Mr. David Fox - OGC
Ms. Jane Axelrad - CDER/OD

ATTACHMENT A:
THE CBC MONITORING PROGRAM

As part of the phase IV postmarketing safety study FDA required of Roche when Ticlid was approved in 1991, the company provided CBC monitoring--a requirement of initiation of ticlopidine therapy--at no charge to patients who did not have insurance or were not covered for testing every two weeks for the first three months of therapy. Following the conclusion of the phase IV study Roche has maintained a CBC monitoring program available to all needy patients taking Ticlid. While patients taking Ticlid may qualify for third party reimbursement for these tests, in the event that they do not, the Roche program is available. Since 1992, Roche has paid for over 52,800 complete blood count ("CBC") tests.

Roche selected SmithKline Beecham ("SB") Clinical Trials to analyze the blood and run the Ticlid monitoring program. Roche and SB Clinical Trials have designed the program to operate in the following way. First, a local Roche representative introduces the doctor to Ticlid and explains the Ticlid monitoring program. If the doctor wishes to use the program, the Roche representative calls SB and gives SB the information needed to enroll the doctor or simply mails or faxes SB the completed enrollment form. Once a physician is registered, there is no limit on the number of patients that that physician may enroll.

The information from the form is keyed into SB's database system. The doctor is assigned an 8-digit account number and SB sends the doctor Ticlid supplies, which include Ticlid requisition forms, slide mailers, large and small red letter bags, a listing of SB collection sites and a Lab Requirement Summary ("LRS"), which provides instructions on completing the requisition and collection, preparing, packaging and transporting the specimen. The doctor completes the patient information section on the requisition form, as instructed in the LRS, and sends one in with every blood sample submitted. Patients take their customized requisition, a copy of the LRS sheet and clinical trials transport bags to the laboratory where the blood work is to be done.

All Ticlid blood samples--from all over the country--are delivered to SB clinical laboratory located in Van Nuys, CA. There, blood samples are analyzed and results sent to the doctor. Blood samples are delivered to the Van Nuys location in one of two ways. If the doctor and patient live in an area near a SB clinical laboratory ("SBCL"), the doctor is given the phone number of that SBCL. When the sample is drawn, the doctor or the draw station calls the local SBCL and has the blood sample and requisition picked up by a SB transport courier. The blood is taken to the local SBCL and then shipped to Van Nuys overnight. If the doctor and

patient do not live near a SBCL, the doctor is given Federal Express supplies, along with the Ticlid supplies, for Federal Express to pick up the specimen and requisition. The Federal Express shipping charge is automatically billed to SB Clinical Trials, not the doctor or patient. Roche is billed for the blood test, not the doctor or the patient. However, the patient is responsible for the cost of drawing the blood (venipuncture/ phlebotomy) and its handling. This charge will vary depending upon the site where the blood is drawn.

The complete test results are sent to the doctor by courier or Federal Express (and, occasionally, US mail). Provided the requisition form is completed correctly, the turnaround time is usually 48 hours. The physician may also request test result information from SB's Client Response Center via the 800 number 48 hours after pickup of the specimen.

ATTACHMENT B:
PATIENT AND PROFESSIONAL EDUCATION PROGRAM

Since its approval in 1991, Roche consistently has maintained an extensive education program for Ticlid. The education program provides educational materials for both patients and healthcare professionals. This program, which is carried out in large part by Roche's national sales force, consists of a series of educational pieces. These materials highlight to healthcare professionals and patients alike the dangers of neutropenia and TTP and how to recognize their signs and symptoms. They also stress the need for vigilance on these important issues.

Over the years, Roche has used various educational materials in connection with the postmarketing education program. 2/ At any one time, Roche sales representatives are distributing a variety of educational materials to doctors and pharmacists. Some are materials to educate these professionals regarding the importance of CBC monitoring. Others are materials for these professionals to distribute to patients. Many of these educational pieces also provide general education on stroke as well as its treatment and prevention. Brochures currently available to patients include: the package insert; the patient package insert; a patient question and answer booklet on stroke; a Ticlid file card; a CBC test schedule magnet; a booklet on required CBC monitoring; a question and answer booklet on stroke, TIAs and Ticlid; and an information booklet on stroke, stroke prevention and Ticlid. Since 1995, Roche sales representatives have ordered over one million pieces of educational material for distribution. Based on the distribution practices of our sales force, we believe that these materials were distributed to approximately 60,000 physicians who prescribe Ticlid--usually in connection with a full presentation regarding Ticlid, including a focus on the required monitoring-- and, subsequently, to patients. A toll free number also is available for patients or professionals to call regarding the CBC monitoring program. Furthermore, in order to respond to telephone inquiries from patients and professionals, Roche Medical Affairs maintains a product information database that encourages the safe and appropriate use of Ticlid.

Roche believes that the keys to success in providing these valuable and potentially life-saving educational efforts are that, in addition to being clearly

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2/ The postmarketing education program has never had an official name, although at various points in time campaigns conducted under this program had such names as the CBC Monitoring Awareness Program and the "Turning Point Program."

written and user-friendly, they have broad reach, are continuous in nature and are provided through several vehicles the facilitate proactive dialogue. These materials directly address the safety of the patient and further enhance the safe use of Ticlid. Based on its submission, Teva apparently does not fully comprehend the safety issues involved or simply is not willing to acknowledge the same.

The education program is important to the safe use of ticlopidine. Roche's market research indicates that currently 91% of physicians surveyed reported being aware of the need for CBC monitoring with Ticlid. Seventy-eight percent were aware of the Roche monitoring program, with 86% of these physicians being aware of the program through their Roche sales representatives. On average, physicians identified two sources for current information on approved Ticlid labeling. Specifically, 85% identified medical journals/medical references and 54% identified the Roche sales representative as their most common source of information. In addition, 40% identified the Roche educational materials as the most common source of current Ticlid labeling. This market research clearly demonstrates the important role both the sales force and the education programs play in the safe and effective use of ticlopidine.